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A Survey of the Presentation of Pharmacogenomic Testing for Psychotropic Medications in Rural Areas

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A SURVEY OF THE PRESENTATION OF PHARMACOGENOMIC TESTING FOR PSYCHOTROPIC MEDICATIONS IN RURAL AREAS

by:
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A thesis submitted to the faculty of the University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College.

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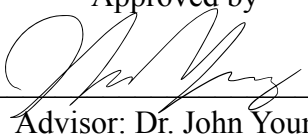
Approved by



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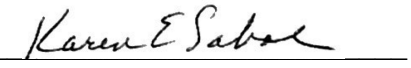

Reader: Dr. Karen Sabol

DEDICATION

To my mom, for encouraging me to always do my best, no matter the task.

To my dad, for showing me there is always a brighter tomorrow.

To my grandparents, for being the best role models anyone could ask for.

To all of my family, for your unconditional support, I love you all.

To my hometown, who participated in my survey, I am so grateful for your contribution.

Without you all, this project would not have been possible.

Thank you from the bottom of my heart.

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ABSTRACT

LAKEN CHEYENNE HANCOCK: A Survey of the Presentation of Pharmacogenomic Testing for Psychotropic Medications in Rural Areas

(Under the direction of Dr. John Young)

The purpose of this research is to assess the knowledge and opinions of the general public in rural areas in regard to genetic testing and pharmacogenomics. 40 people from self-identified rural areas participated in this study by completing an online Qualtrics questionnaire and an in-person or online semi-structured qualitative interview. The Qualtrics questionnaire measured demographic information, as well as depression, anxiety, stress, positive affect, and negative affect using the Depression, Anxiety, and Stress Scale-21 (DASS-21) and the Positive and Negative Affect Scale (PANAS) measures. The semi-structured qualitative interview included questions pertaining to the decision support tool (DST) presented to participants, as well as health-care preferences and likelihoods of pursuing specific strategies of intervention. Overall, results indicated that the position of drugs within the DST visual framework had an effect on respondents' medication preferences. Qualitative data also suggested that these decisions were made in the context of relatively little knowledge. In addition, participants indicated further details such as side effects, medication ingredients, costs, addiction statistics, possible medication interactions, dosages, and previous controlled clinical trial results as information they would find helpful. Results from the study can be used to improve the implementation of pharmacogenomic testing within rural medical settings.

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Introduction

What is Pharmacogenomics?

Pharmacogenomics studies the role that genetics plays within a person's physical and chemical response to pharmaceutical medications (Abul-Husn, Owusu Obeng, Sanderson, Gottesman, & Scott, 2014; Abul-Husn. & Kenny, 2019). Through the role of pharmacogenomics and genetic testing, personalized medicine has gained the potential to be utilized for widespread medicinal treatments in the future. Genetic information can now be combined with the concept of personalized medicine, which includes using a patient's genetic testing results to see which medications are more likely to be effective with minimal adverse effects for the individual patient (Abul-Husn. & Kenny, 2019). In fact, many medications now include Food and Drug Administration (FDA) pharmacogenomic labeling information (Schuck, Marek, Rogers, & Pacanowski, 2019; Young, Bhattacharya, Ramachandran, Lee, & Bentley, 2021; Young, Jimenez, Pruett, & Hancock, 2021). Drug metabolism, unique side effects, and non-responsiveness to medication are among the many personalized reactions that can be identified and potentially customized to ensure a more optimal treatment outcome for individual patients (Abul-Husn, & Kenny, 2019; Young, et al. 2021). In addition, precision medicine provides the potential to decrease healthcare costs as opposed to the current method of physicians prescribing medications by base rate experiences, which are often based on personal anecdotal accounts.

Pharmacogenomic History

The idea of personalized medicine began in the late 90s and has since built a foundation for better understanding treatment of diseases using genome sequencing, which has been aided

by data collection through electronic health records (Abul-Husn & Kenny, 2019). Additionally, genomic testing can reveal genetic proclivities to develop certain diseases, some of which are identifiable by single gene markers (Abul-Husn & Kenny, 2019). With this innovation, carriers of these disease variants can take additional steps to decrease their likelihood of developing symptoms of the disease many years in advance, as well as make more informed decisions about the propagation of those genes in future offspring. Despite rapid advances in this area of research and technology development, genome sequencing remains a developing process with somewhat imprecise application to only a few narrow dimensions of disease and disease variants.

The uptake of pharmacogenomics in clinical healthcare settings is relatively slow in comparison to other medical breakthroughs and techniques, with most applications in use being attributed to oncology due to comprehensible somatic mutations and distinct gene markers (Lunshof & Gurwitz, 2012). Although there are several reasons for the seemingly stagnant process, Amstutz and Carleton (2011) cited the imperative need for evidence-based clinical practice guidelines for pharmacogenomics prior to widespread implementation in clinical settings (Lunshof & Gurwitz, 2012; Nickola, Green, Harralson, & O'Brien, 2012). Likewise, private sector drug companies have typically been disinterested due to lack of economic incentives to administer or invest in pharmacogenomic testing as part of decision making within controlled trials (Lunshof & Gurwitz, 2012). Lack of education for healthcare professionals also promotes difficulty with objectivity and integration of the use of test results in clinical practice settings (Lunshof & Gurwitz, 2012). Additionally, it is notable that post-graduate pharmacogenomic training remains a pressing issue, as only 10% of a sample of 10,303 United States physicians reported the perception that they were adequately knowledgeable about genetic testing and pharmacogenetic implementation for patient treatment (Nickola et al., 2012).

Likewise, a 2012 study of practicing nurses reported that only 30% of nurses had received continuing education in genetics in the past two years (Thompson & Brooks, 2011). Pharmacists, however, have shown substantially higher reports of positive attitudes towards pharmacogenomics compared to physicians, and as a group are more willing to undergo educational training related to pharmacogenomic principles (Nagy, Eirini Tsermpini, Siamoglou, & Patrinos, 2020).

Although this openness to continuing education is useful and necessary for long-time healthcare professionals, studies have also shown that health professional schools have not generally updated genetic and genomic academic material to include the most recent implementations of pharmacogenomics (Nickola et al., 2012). In a 2010 survey, for example, 76% of the 90 program respondents among United States and Canadian medical schools indicated that their pharmacogenomic education was "poor" or "not adequate at all" (Nickola et al., 2012). Likewise, a study of pharmaceutical schools found that while 89% of schools included at least some pharmacogenomics education, less than half (47%) intended to increase their amount of pharmacogenomics curriculum in the next three years (Nickola et al., 2012). Research geared toward improving pharmacogenomic education suggests that the movement should be prioritized and facilitated by pharmacists (as of 2020 over 50% of clinical sites offering pharmacogenetic testing were pharmacist-led; Nagy et al., 2020; Nickola et al., 2012). Possible methods of advancing continuing education in this domain include requiring pharmacogenomic-relevant hours for licensure renewals, increasing undergraduate and health professional school education, and incorporating all members of patient care teams in the implementation of pharmacogenomics and precision medicine through a multidisciplinary approach (Nagy et al., 2020; Nickola et al., 2012; Tsermpini et al., 2019).

Rural Medicine

As of the 2017 Census, 60 million people, or 1 in 5 Americans lived in rural areas where access to health-care has been measurably limited and among the primary issues cited as problematic about rural life (Greenberg, Haney, Blake, Moser, & Hesse, 2017; Nasser, 2021). Based on a survey of 250 health-care quality indicators, one in ten of these indicators have worsened from 2000 to 2015 in rural areas, signifying the potential distal impacts of limited access to adequate health-care services (Pourat et al., 2020). Additionally, rural residents are more likely to lack a high-school education, rely on Medicaid coverage, fall in the United States Federal low-income bracket, and have a poorer health status compared to urban areas (Pourat et al., 2020). Further, Health and Resources Administration (HRSA) Health centers are the most prominent or only source of medical service in many areas with the majority of patients being older, white, female, obese, and uninsured compared to the general rural population, and with a higher patient-to-physician ratio than notable in urban areas (Pourat et al., 2020). Health literacy and access to health information technologies are also issues in rural communities, partially due to two-thirds of rural counties being at or above the national poverty average (14.4%; Greenberg, Haney, Blake, Moser, & Hesse, 2017). Specifically, most rural areas have limited internet access and poor connection quality, which not only leave residents disadvantaged to the uses of telehealth, but also health information technology (HIT) that helps monitor and self-regulate one's health (Greenberg, Haney, Blake, Moser, & Hesse, 2017).

The local context provides salient examples of these phenomena, given that Mississippi was ranked 47th among states in 2021 by the United Health Foundation for the following four health measures: outcome (number of health-related deaths, mental and behavioral health [e.g., excessive drinking, depression, and non-medical drug use], and physical health [with emphasis

on chronic conditions]), behaviors (sleep health, sexual health, nutrition and exercise, and tobacco use), clinical care (access to care, preventative services, and quality of services), and community and environment (community safety, economic support, social structure, education, air and water pollution, climate change, and transit; Connell, Wang, Crook, & Yadrick, 2019; Explore health measures in Mississippi, 2021). In a study conducted in the Mississippi Delta, participants cited structural barriers including transportation, lack of insurance, anticipated cost of services, and insufficiency of healthcare availability or specialists as barriers to health-care utilization (Connell et al., 2019). Likewise, other structural barriers include interpersonal factors like lack of social support, fear of stigmas associated with disease and diagnosis, and fear of health-care providers breaking confidentiality agreements (Connell et al., 2019).

In these rural communities, mental health is a major concern as substance abuse and mental health difficulties are inordinately high. Compared to urban counties, suicide rates are over 1.5 times higher (Summers-Gabr, 2020). Resources for mental health including psychiatrists, psychologists, psychiatric nurse practitioners, and therapists are practically non-existent in most rural areas as fewer than 10% provide services in rural settings (Hoeft, Fortney, Patel, & Unützer, 2017). As a result, rural residents often only seek clinical mental health consultation from their primary care providers and may be more likely to seek help in non-clinical settings (e.g., friends, family, or spiritual guidance; Hoeft et al., 2017).

As a result of the COVID-19 pandemic, mental health issues increased, particularly depression (potentially due to increased social isolation, fear of illness, sudden loss of family members, job layoffs, and dramatic change in everyday lifestyle; Diamond & Byrd, 2020; Matias, Dominski, & Marks, 2020). In order to better serve rural areas, telehealth medicine has become increasingly more popular in rural settings (Hoeft et al., 2017). With regard to the

current study, it is potentially relevant to note that Mississippi began a telegenetics clinic in an effort to reach rural populations, which Medicaid and all private insurers operating within the state are legally required to cover (Boothe & Kaplan, 2017). This program is not widely known, however, and can only serve a small number of patients due to limited availability (Boothe & Kaplan, 2017). Due to socioeconomic statuses, lack of technological education, and isolated areas without access to broadband internet, telehealth opportunities are not ideal or accessible for all residents of rural areas. As a result, many mental health conditions remain undiagnosed or untreated in rural areas and eventually lead to hospitalizations in many cases, especially among children (Bettenhausen et al., 2021). In addition to the lack of proper mental healthcare access, rural physicians often feel unequipped for adequate treatment.

In general, this lack of resources leads to primary care providers being the go-to source for all rural residents' healthcare needs, including psychiatric (Avery, Dwan, Sowden, & Duncan, 2020). The interventions employed in this context are overwhelmingly biomedical, meaning that they have some propensity to be affected by genetic structure (consistent with pharmacogenomics research). This could be beneficial in some cases, although research suggests that current consultations on genetic testing often leave people feeling like they have received inadequate information due to limited healthcare literacy and lack of further explanations being offered about complex genetic concepts (Barton, Wingerson, Barzilay, & Tabor, 2018). Yanes et al., for example, cited common reactions of anxiety, fear, frustration, isolation, and uncertainty following the receival of genetic testing results (Yanes, Humphreys, McInerney-Leo, & Biesecker, 2016). Extensive consultation training should be implemented in clinical practice to reduce these fears, as many patients are currently seeking the majority of support and understanding from online platforms and media sources, which commonly display

misinformation and biases (Barton et al., 2018). Unfortunately, research in this domain has been limited and the most optimal methods of communication about pharmacogenomic results are as yet unknown.

Pharmacogenomics for Mental Health in Rural Areas

Pharmacogenomic testing has been studied with various psychotropic medications, where these techniques have been shown to be beneficial to treatment outcome (particularly with antidepressants; Schuck et al., 2019). Because most people in rural areas with depression or anxiety do not have access to specialty mental health resources, they disproportionately see their primary care physicians when they seek help for emotional symptoms. In this non-specialized environment, pharmacogenomic testing could provide numerous advantages to guide treatment. For example, pharmacogenomic testing for anxiety and depression can remove the usual "trial and error" work in seeking the appropriate prescription for a given individual (Schuck et al., 2019). As an example, for Major Depressive Disorder (MDD), 30 to 50% of patients did not respond to their first prescribed medication treatment when treated without the benefit of not using pharmacogenomic testing, a rate that was significantly diminished in a randomized sample of people who received testing at treatment onset (Yoshida, Müller, & Kennedy, 2019). Based on a previous study between treatment of patients with depression guided by pharmacogenomic testing and unguided (standard treatment), remission rates of those with pharmacogenomic testing were also significantly higher (OR 1.7; Schuck et al., 2019; Yoshida, Müller, & Kennedy, 2019). Thus, there is some randomized evidence to suggest that pharmacogenomic testing could improve treatment outcomes in general settings (such as those typically encountered in rural settings) among people experiencing mental health concerns.

Clinical Implementation

Given the potential benefits and rapidly increasing applied use of pharmacogenomic tests, additional research on their implementation, utilization, and refinement is imperative. In particular, understanding patient responses to the in-clinic presentation and administration of genetic testing and pharmacogenomic results is necessary to understand the interpretation and applied use of these tests. Without demonstrable evidence of clinician and/or patient understanding of the outcomes of these tests, which are often very difficult to interpret, their use may confound treatment decision-making rather than improve it. In general, there is also evidence that patients do not easily tolerate changes in typical treatment procedures (which are often defined by their own stereotypes of physician-patient interaction). For example, Abul-Husn and colleagues (2014) proposed three questions to consider when discussing how to establish an acceptable reputation for a new-to-patient treatment plan that involves genetic data (Abul-Husn et al., 2014). The questions are as follows: "Are patients open to and interested in receiving personalized genetic testing information? What is the effect of personalized genetic testing information on psychological well-being? Does personalized genetic testing information motivate patients to improve their health-related behaviors?" (Abul-Husn et al., 2014) Through their research of a group of compiled studies, the team concluded that patients have an overall positive attitude towards undergoing pharmacogenomic testing, and their willingness increased with the severity of the diseases being tested (Abul-Husn et al., 2014). However, the authors also indicated that not many studies had been conducted on the topic, and clarity of the patient's role in the process was limited (Abul-Husn et al., 2014).

Cost efficiency also remains uncertain with regards to the value of conducting pharmacogenomic testing on each patient prior to beginning treatment (Schuck et al., 2019).

Many insurance companies like Medicare classify these drug-gene interaction tests as preliminary and provide little or no reimbursement in their healthcare plans, making the feasibility of accessing tests more limited when considering all potential patients (Keeling et al., 2019). These conditions could be changing, though, as knowledge of these techniques becomes more widespread. In a 2019 Keeling et al. study, for example, insurance payers stated that they valued the information published by the Clinical Pharmacogenetic Implementation Consortium (CPIC) for pharmacogenomic information, which could be informative in encouraging insurance companies to adopt preemptive pharmacogenetic testing into coverage policies (Keeling et al., 2019). This consortium regularly reviews and issues policy statements concerning the effectiveness of various pharmacogenomic tests for specific classes of medications, potentially making it a valuable resource in future dissemination of these techniques.

Current Pharmacogenomic Presentation

Lack of federal health guidelines for pharmacogenomic testing is cited as a common barrier for clinical implementation of pharmacogenomic decision making. As of 2018, 19 guidelines over 44 drug-gene interactions had been published by the CPIC (Beckett, Kisor, Smith, & Vonada, 2018; Relling & Klein, 2011). These guidelines aim to assist physicians and other healthcare providers who are not formally trained in pharmacogenomics. In their literary analysis of guidelines, Beckett et al. (2018) found that only 3 of 49 peer-reviewed articles addressed therapeutic guidelines for psychiatry. While these guidelines use evidence-based approaches for instruction, they do not cover all possibilities, and ambiguity is a result of experience and a care provider's own individualized approaches (most of which do not entail a strong knowledge of genetics or genetic testing; Beckett et al., 2018).

Although there is not a specific clinical approach found to be the most appropriate for timing of pharmacogenomic testing and delivery methods of results to patients, there are multiple adequate approaches that can be modeled. While testing can be executed preemptively or when the need arises, many clinicians propose an interdisciplinary testing approach that could be standardized (Zierhut et al., 2017). In order to keep patients informed on the process, some healthcare advisors suggest that a pretest and posttest counseling session should be administered for patients, while others in clinical settings deem this unnecessary in gauging patient clarity and understanding (Zierhut et al., 2017).

Given the complexity of tests and lack of clinical standards, there are several beneficial decision support tools (DST) available to aid clinicians seeking to utilize pharmacogenomic tests in practice. One of the most prevalent is from Genesight, which provides a visual interpretation tool to assist health-care providers who lack confident education and experience in pharmacogenomics (Pyzocha, 2021). The actual GeneSight genetic test currently analyzes 57 neuropsychiatric medications and 12 genes with a measurable 100% accuracy rate at a molecular genetic level (Pyzocha, 2021). As a visual aid for patients and providers, the test categorizes risks of medications by a green, yellow, and red color code. The green code indicates a use as directed approach (low risk), yellow signifies a moderate gene-drug interaction (moderate risk), and red cautions significant gene-drug interactions (high risk; Pyzocha, 2021). In addition to the yellow and red color codings, these two sections are also broken down into subsections indicating further cautions or instructions for the healthcare provider, including high or low dosage warnings, adverse side effect risks, and conflicting dose adjustments due to the patient's metabolism (Pyzocha, 2021). While the GeneSight test can be administered at home, only physicians registered through the GeneSight database are able to order the test for a patient,

unlike many commercial genetic testing kits (Pyzocha, 2021). However, misconception of the prediction of treatment effectiveness may be skewed in patient understanding, so test result analysis should be interpreted and ultimately used as a resource for decision-making rather than the treatment standard (Pyzocha, 2021). Although it is not currently FDA approved, Medicare fully covers the $1,569 cost of the test, and other private providers typically cover $1,239 or more of the cost of testing (Pyzocha, 2021).

Purpose of Current Study

On account of the literature reviewed, this study has been designed to evaluate the opinions of the general public in rural areas in regard to genetic testing and pharmacogenomics. A previous study conducted by surveying students at the University of Mississippi collected data on the presentation of genetic testing; however, the surveyed sample was not representative of a primary care setting because the majority of respondents were recruited from psychology classes and were more knowledgeable than the general public on the topic of pharmacogenomics (Young et al., 2021). Thus, this study will analyze rural residents' opinions on genetic testing and using their personalized results to make healthcare decisions, as well as their understanding of pharmacogenomic testing results. Likewise, this study will help future researchers determine what should be discussed during a consultation regarding genetic testing, and potentially develop insights about how pharmacogenomic test results could ideally be presented in order to receive a positive response in rural communities.

Methods

Participants

For this study, residents of rural areas were recruited. A total of 40 people participated, 27 of whom were male (67.5%) and 13 of whom were female (32.5%). Participant age ranged from 18 to 88 years of age, with the average being 38.80 (SD = 21.62). The modal participant was 21 years old (n = 8; 20%) and Caucasian (n = 38; 95%). Participants were recruited by word of mouth in and around Waynesboro, Mississippi (the author's hometown), although some participants were from rural areas of Tennessee, Georgia, and Alabama (with ties to Mississippi that facilitated their recruitment to this study). Participants received no compensation or incentives for participation. Interviews for the study were conducted in person and online through Zoom video conferencing, which was left to the discretion of the participant due to the COVID-19 pandemic. Living in a self-reported rural hometown was the only limiting criterion for participation in this study. Education level of participants ranged from middle school or less (n = 2; 5%) to graduate degrees (n = 2; 5%). The most common report of education level was "Some College" (n = 16; 40%). The education level of each participant's parents was also reported, and the levels ranged from middle school (n = 8; 10%) or less to doctorate degrees (n = 1; 1.25%). The modal level of education for participants' parents was high school (n = 38; 47.5%). Additionally, 17 participants (42.5%) reported that they were parents (step-parent, foster parent, or any other type of guardian was included in this description). Prior to the recruitment of participants, Institutional Review Board approval was obtained for the study.

Measures

Through the course of this study, each participant's responses were measured through three different analyses. A Qualtrics survey was used to collect self-report data and participant's background information. This entailed administration of the two measures outlined below, which was followed by a more in-depth interview about individuals' perceptions of pharmacogenomic testing using an applied analogue method previously implemented in local studies conducted in the same lab.

Depression, Anxiety, and Stress Scales, 21-Item Version (DASS-21). The DASS-21 is the shortened version of the original *Depression, Anxiety, and Stress Scales, 42-Item Version (DASS-42)* and is designed to measure anxiety, depression, and stress over a period of two weeks (Young et al., 2021; Osman et al., 2012). The 21 question survey is divided into three sub-scales to indicate the presence of anxiety and depressive disorders through a four-point Likert-type scale (Young et al., 2021; Osman et al., 2012). Response choices are designed to rate how much a participant agrees or disagrees with a statement or how the participant feels that the description applies to them (Sullivan & Artino, 2013). Previous research has indicated that the instrument has strong psychometric properties confirmed by both exploratory and confirmatory factor analysis. Reliability levels confirmed by internal consistencies were relatively high (depression 0.91; anxiety 0.81; stress 0.9; Lovibond & Lovibond, 1995). The DASS-21 also has known norms (Lovibond & Lovibond, 1995). The instrument appears in Appendix 1.

Positive and Negative Affect Scales (PANAS). The second measurement used through the Qualtrics survey is The Positive and Negative Affect Scales (PANAS). The PANAS scale used in this study has the ability to measure both positive and negative affect over the past week using a five-point Likert-type scale (Young et al., 2021). For the specific questionnaire,

participants indicated their opinions through “Strongly Disagree, Mildly Disagree, Neither Agree nor Disagree, Mildly Agree, Strongly Agree” options to the questions shown in Appendix 2. Research conducted testing the reliability of the PANAS scale found the tool to have high internal consistency defined by alpha coefficients for positive and negative affect (PA 0.86; NA 0.87; correlation 0.09; Watson, Clark, & Tellegen, 1988). There are also established norms for the PANAS tool (Watson, Clark, & Tellegen, 1988).

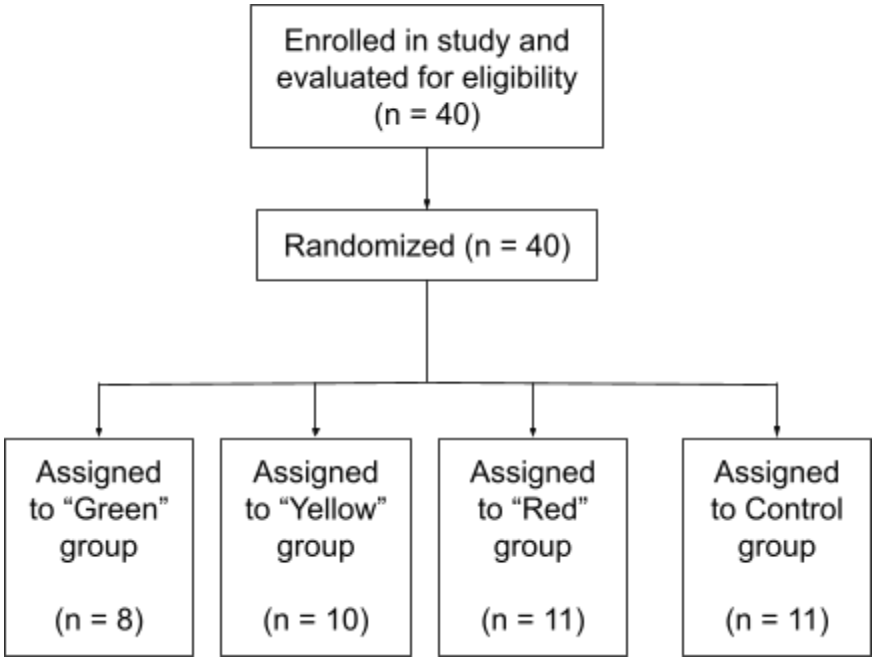
Semi-structured qualitative interview. The final measure, which was administered by the researcher, was a semi-structured qualitative interview shown in Appendix 3. The interview questions used in this study were an adaptation of the survey questionnaire utilized in a study by Young et al. (2021), which is currently under review for publication (Young et al., 2021). Consistent with the desire to learn more about these issues in rural populations, questions regarding rural health-care were added to the questionnaire. The interview-style questionnaire was designed to assess confusion, concerns, and approval indications through broad likelihood, opinionated, or rank style questions. It was administered following a standardized presentation of genetic results, which were fabricated but done using a template based on the commercially available GeneSight tool, which has been used in numerous studies. The DST used was color-coded green, yellow, and red (mirroring GeneSight’s risk-color association). It displayed both brand and generic names for each medication but did not include any other information. Additionally, fluoxetine/Prozac was used as the target of manipulation due to the identifiability of the medication.

Procedure

Participants first responded to the Qualtrics questionnaire containing the demographic, DASS-21, and PANAS parameters. The questionnaire was completed in the presence of the

researcher each time either in-person or through the online program Zoom. By completing the Qualtrics survey, participants' consent to participate was indicated. Participants were notified that they were not required to answer any questions that made them uncomfortable and could opt out of the study at any time. Following the Qualtrics questionnaire, participants were randomly assigned to groups (one control group and three experimental groups). The randomized sample assignments are displayed in Figure 1. To begin the semi-structured qualitative interview, participants were read a prompt and given a sample DST that coordinated with their assigned group. Each DST dashboard maintained the same medications, but fluoxetine's placement in the DST differed between green, yellow, and red categories. A sample dashboard is displayed in Appendix 4.

Figure 1. Participant assignments



The prompt for the semi-structured qualitative interview remained the same across each experimental cohort, but the control group was not told that fluoxetine was the most recommended for the participant's age group. The prompt is similar to the statement used in a

study by Young et al.; however, depression in the prompt has been replaced with anxiety for this study (Young et al., 2021). The prompt for the experimental groups is shown below:

> I want you to pretend that you have a lot of anxiety and went to see a psychiatrist, who suggested that you should undergo genetic testing before starting any medication. As the psychiatrist explained, this testing looks at your genetic code and predicts which medications are likely to work best and worst. I'm going to give you a feedback form that shows the results of this genetic testing. It's pretty similar to how some of these forms actually look, and all the medications listed are real. Even though the results are fake, think of them as though they were the real results of your own genetic testing. Also, be aware that the most commonly prescribed medication for anxiety for people in your age group is fluoxetine/Prozac. Take a minute to look over the form and learn what you can, and then I'll ask you a few questions about your reactions.

After the prompt was read to each participant, they were asked to select a medication from the dashboard that they would choose to take based on their interpretation of the DST and the prompt (despite whether or not using medication aligns with their personal dispositions). After choosing a medication, participants were asked a series of questions that were constant across each group. Most of these questions were structured to encourage dialogue and any additional information the participants wanted to add. However, two questions were polar interrogatives and one question was a rank-order question to better quantify data on health resource availability and preference for mental health treatment.

Data Analysis

A Chi-square test of independence was conducted between the "green", "yellow", and "red groups", and once again in reference to the control and "yellow" groups. The Chi-square test of independence was conducted with the assumption that all categorical variables were mutually exclusive and were equal in chosen probability. Demographic variables and qualitative

information were quantified and their frequencies were calculated. The “Results” section highlights all outliers of the analysis.

Results

A summation of the frequency of each drug category ("green", "yellow", and "red") chosen can be seen below in Table 1. The Chi-Square comparisons across each drug category indicate that there is a significant difference in the frequency of which drugs were selected within each category (X^2 (4) = 12789 $p < 0.001$). In each group, the "green" medication category was chosen the majority of the time; 87.50% (n = 7) chose the "green" category in the "green" participant group (low risk), 60% (n = 6) chose the "green" category for the "yellow" participant group (moderate risk), 63.64% (n = 7) chose the "green" category for the "red" participant group (high risk), and 72.73% chose the "green" category for the control group. Fluoxetine, also listed as the brand-name medication on the DST, was most commonly chosen as the medication preference in the "green" participant group (87.50%; n = 7), which listed fluoxetine in the "green" low-risk category.

Table 1. Medication categories chosen by each group

Participant Group	Medication Category Chosen		
	Green	Yellow	Red
Green[a]	7	0	1
Yellow[b]	6	3	1
Red[c]	7	2	2
Control[d]	8	3	0

[a]chose fluoxetine (87.5%); [b]chose fluoxetine (30%); [c]chose fluoxetine (9.09%); [d]chose fluoxetine (18.19%)

The one participant in the "green" group explained that a "red" category medication was chosen because the participant was familiar with the drug chosen. Additionally, the participant interpreted the "red" category label ("use with increased caution and with more frequent monitoring") as the participant receiving frequent monitoring by physicians, which the participant expressed a desire to have. Most of the "yellow" and "red" participants chose medications that were not labeled in the "green" category due to fluoxetine's placement in the DST. The three participants who chose medications in the "yellow" categories within the control group (who were not notified of any prescription base rates) each had varying answers to explain their choice. One participant chose the "yellow" category description ("use with caution") because they always used caution with medications and interpreted the "yellow" category to be the best fit for them. Another participant explained they perceived the riskiest medications to be the most effective, however, they would not be willing to try the most risk-inclined ("red") group, and they perceived the "green" group to not be effective enough. This reasoning was also cited one other time throughout the study for a separate participant category. The final participant to choose a "yellow" category medication made their decision based on familiarity with the medications. When comparing the "yellow" category and the control group, no differences were shown in the frequency of medication selection (X^2 (2) = 1.24; p = 0.54). 50% of participants (n = 20) stated that without the color coding indicators in the DST, they would have chosen a different medication, mostly at random. Those who would choose the same medication (50%; n = 20) most commonly stated that they chose the medication that they were the most familiar with.

The mean comparisons (ANOVAs) of the DASS-21 (depression, anxiety, and stress) and PANAS (positive and negative affect) scores are displayed in Table 2. Overall, all participants

were within normal limits for positive affect, however, 13 participants (32.5%) were at least one standard deviation above the mean for negative affect. Only a few participant scores were elevated for symptoms of anxiety (1 severe and 1 moderate), depression (1 moderate), or stress (1 moderate). Because participant scores remained in normal limits for the majority and did not differ across groups, these measures were unlikely to affect participants' responses to the survey questions.

Table 2. PANAS and DASS-21 Self Report Scores

Measure	Mean (σ)
Depression	3.18 (3.98)
Anxiety	2.63 (3.61)
Stress	5.53 (4.60)
Positive Affect	32.05 (6.64)
Negative Affect	12.13 (9.11)

For the quantitative data in the semi-structured qualitative interview, the average likelihood of taking medication (61.08%) to treat clinically diagnosed anxiety was higher than the likelihood of attending therapy (53.38%). Participants most commonly referenced fear of addiction and negative effects as reasons for their disinterest in medication, while stigma and fear of judgment were reported reasons for the concerns with therapy. In addition, the average likelihood of undergoing genetic testing was 55.88%; however, 48 participants (96%) indicated that they would be more likely to undergo genetic testing if the tests were to predict serious illnesses or traits that they might pass on to their children. The two participants who said their likelihood would not be changed indicated that there was a 0% likelihood of undergoing genetic testing under any circumstances. These likelihoods are referenced in Table 3.

Table 3. Quantitative summary of likelihoods from the semi-structured qualitative interview

Circumstance	Percentage of Likelihood
Medication	61.08%
Therapy	53.38%
Genetic Testing	55.88%

Despite the lower likelihood score of attending therapy, 18 participants (45%) indicated that they believed therapy to be superior rather than medication (question 4 on the interview questionnaire), while only 11 participants (27.5%) viewed medication as superior and 11 participants (27.5%) felt that neither were superior. In addition, 21 (52.5%) participants stated that they would not take medication in conjunction with therapy, 12 (30%) participants expressed no concern and were willing to take medication while attending therapy, and 7 participants (17.5%) stated that if they needed (as indicated by their physician) to take medication at the same time, they would have no objections to doing so.

Information gathered in response to questions 10, 11, 12, and 13 surveyed health-care preferences and accessibility. Of the participants surveyed, 80% (n = 32) reported that they travel to a different city for access to health-care. In addition, 20% of participants (n = 8) were able to name a mental health resource in their hometown other than their primary care physician. These resources include the following: mental health facilities (n = 3), counselors (n = 3), health departments (n = 2), and psychiatrists (n = 1). When given the choice between consulting a psychiatrist or primary care physician for the participant's first visit regarding mental health, 80% of participants (n = 32) said they would visit their primary care physician first. The rank order question surveyed where participants would choose to go for help if they had severe anxiety. The full frequency measure can be viewed below in Table 4.

Table 4. Quantitative data for the rank-order interview question (Question #12)

1st Choice		**2nd Choice**		**3rd Choice**	
Psychiatrist	0	Psychiatrist	4	Psychiatrist	5
Psychologist	1	Psychologist	0	Psychologist	5
Therapist	3	Therapist	4	Therapist	8
Primary Care Physician	10	Primary Care Physician	15	Primary Care Physician	11
Friends & Family	11	Friends & Family	13	Friends & Family	5
Online Resources	15	Online Resources	4	Online Resources	6
4th Choice		**5th Choice**		**6th Choice**	
Psychiatrist	8	Psychiatrist	12	Psychiatrist	11
Psychologist	11	Psychologist	16	Psychologist	7
Therapist	17	Therapist	4	Therapist	4
Primary Care Physician	2	Primary Care Physician	2	Primary Care Physician	0
Friends & Family	1	Friends & Family	3	Friends & Family	7
Online Resources	1	Online Resources	3	Online Resources	11

For the qualitative interview, participants commonly expressed the desire to research the medications online, talk to others who have taken the medications, or consult their primary care physician before choosing a medication from the DST. Participants commonly noted that beyond the name of the medications, they would also like to know side effects, medication costs, addiction statistics, dosages, interactions with other medications, and if the medication is a

selective serotonin reuptake inhibitor (SSRI). Lifestyle change, removing stressors, breathing and relaxation techniques, healthy dieting, herbal medicine, exercise, and religion were among the most common ways participants would try to address anxiety aside from medication and therapy. When participants were asked how they may respond if they received a DST with only medications in the "red" category, most indicated they would experience frustration, sadness, or hopelessness, but would be more willing to seek other treatments like therapy. In addition, the majority of participants stated that they would like a second opinion fromanother healthcare provider. Only 11 participants (27.5%) expressed a specific concern regarding genetic testing; these included: lack of knowledge, possibility of discovering deadly disease, legal privacy and ownership of test results, and pharmacogenomic testing reliability.

Discussion

The results of this study show that the DST organization of psychotropic medications had a significant influence on the decisions of the participants. This is particularly true when the base rates of fluoxetine aligned with the "green" category of the DST, as 87.5% of participants chose a medication in the "green" category, which is a higher percentage than any other category or participant group. Several participants misinterpreted the color-coding of the DST, and while this could be a representation of limited health literacy in rural areas, this may also be attributed to the method of presentation of the DST, which was designed to be implemented in a clinical setting with the assistance of a (at least somewhat) knowledgeable provider. Despite the success of the DST coding, many still chose their medications based on base rate, which could imply participant's discomfort in making their own health-care decisions or previous familiarity with the medication (fluoxetine was the most well-known medication overall). However, 50% of participants depended solely on the DST as they indicated that without the color-coding, they would have picked a medication completely at random. So while confidence in using pharmacogenomic indicators to make decisions needs improvement through education for patients and training for health-care providers, the implementation of using a DST for decision making is still accepted by a large number of participants (particularly considering the disadvantaged factors of rural areas and relative lack of familiarity with these techniques).

Willingness to undergo genetic testing also yielded a low percentage of participants overall (55. 88%). While those who expressed apprehensions toward genetic testing noted concerns of privacy, possibility of fatal genetic diseases, and reliability, 29 participants reported

that they did not have any concerns, and while 12 participants indicated that they were 100% willing to undergo genetic testing, 17 participants remained who were 100% unwilling to undergo genetic testing but referenced no specific concerns. Not referencing specific concerns can be indications of negative stigma surrounding genetic testing due to misconceptions, although this is speculative and the reasons for their adamant position against genetic testing were not entirely clear.

Rural area education disparities were also consistent with previous research, with the majority of participants having the highest degree of a high school diploma and some college courses. The highest level of education of the participants' parents was most commonly identified as high school (with many not receiving high school diplomas). While participants most commonly possessed a higher level of education than their parents, it is important to note parental education levels because if parents did not receive a high education level or have high levels of health literacy, then participants would be likely to lack additional relevant learning resources during their early development (e.g., home learning environment), which could affect their orientation to the questions posed in this study.

Throughout the semi-structured qualitative interview survey, an extreme reference to primary care physicians was made, which can be explained by the lack of health resources in rural areas that lead primary care physicians to take on many roles. Reliance on primary care was demonstrated for many to be attributable to a lack of health-care resources, which was confirmed by the large percentage (80%) of participants traveling to different cities for any health-care access. In addition, in response to the rank-order question, no participants chose to see a psychiatrist as their first choice, and only one chose to seek a psychologist. Generic "online resources" were the most common selection for participants' first choice, which is not ideal

considering the amount of misguided health information that is accessible on the Internet. While this was the most preferred resource, many also cited the lack of reliability of online information, and as a result, 11 participants chose online resources as their last resource choice. Participants most often chose to seek guidance from therapists, psychiatrists, and psychologists as their last options (4th, 5th, and 6th choices). Reasons for this include limited access (only one participant cited the access of a psychiatrist in their hometown) and preference (80% of participants stated they would rather seek assistance from the primary care physician than a psychiatrist for their first consultation regarding mental health). In addition, those who were able to name therapy resources in their hometown often said they would refrain from visiting them due to fear of a privacy breach. This concern of privacy remains a large interpersonal factor in seeking medical services in rural areas as the fear was also cited in a study conducted in the Mississippi Delta (Connell et al., 2019).

After reviewing participants' concerns, confusions, and recommendations, beneficial information for in-clinic implementation of pharmacogenomic testing and decision-making could be discerned. Overall, more explanations of the physical testing process are likely needed alongside informing the patient of confidentiality policies, given respondents' apprehension about the method of testing. Additionally, pre- and post-testing consultation proposed by previous research would be beneficial to offer in order to alleviate fears of genetic testing and emotionally processing the results (Zierhut et al., 2017). Finally, participants indicated that in addition to the DST, information provided to patients should include side effects, medication ingredients, dosages, possible medication interactions, addiction statistics, costs, and previous controlled clinical trial results.

Limitations

Due to the demographics of the geographic region participants were recruited from, the study lacked diversity in race and ethnicity. In addition, socioeconomic statuses were not measured. Differing socioeconomic statuses may affect access to healthcare, previous education levels, health literacy, and opinions on health care providers, which could substantially influence results. The small sample size of this study and localized data also limited the generalizability to outside regions and states.

Future research

Significance for future research includes broadening the scope of participant recruitment and surveying a larger number of females to determine the influence that gender may have on the perception of genetic testing. In addition, this study chose to use the hypothetical diagnosis of anxiety in order to obtain the most transparent results. However, substituting the word "depression" in the script for "anxiety" may also be implemented to test the effect of the more negative connotations of depression in a rural area. Future studies could also manipulate the setup of the experiment, including using a less commonly known drug for the base rate in the prompts.

Personal Reflection

Upon beginning this study, I possessed a strong desire to become a physician in a rural area, due to witnessing the effects of health-care scarcities in my own rural community. I chose to survey my rural community after witnessing multiple friends and family members struggle with mental health diagnoses. As a result of conducting this study and analyzing the data, I have acquired an increased motivation to help educate my community (and hopefully beyond) on the positive benefits of pharmacogenomic testing as well as improve health literacy. In addition, I endeavor to one day become a rural physician who remembers the need for continued education and collaboration with mental health experts in order to give patients the best care possible.

APPENDIX 1

Depression, Anxiety, and Stress Scales, 21-Item Version (DASS-21)

Please indicate how much you agree with each of the following statements, or how true it is about you.

	Strongly Disagree	Mildly Disagree	Neither Agree nor Disagree	Mildly Agree	Strongly Agree
Interested	○	○	○	○	○
Distressed	○	○	○	○	○
Excited	○	○	○	○	○
Upset	○	○	○	○	○
Strong	○	○	○	○	○
Guilty	○	○	○	○	○
Scared	○	○	○	○	○
	Strongly Disagree	Mildly Disagree	Neither Agree nor Disagree	Mildly Agree	Strongly Agree
Hostile	○	○	○	○	○
Enthusiastic	○	○	○	○	○
Proud	○	○	○	○	○
Irritable	○	○	○	○	○
Alert	○	○	○	○	○
Ashamed	○	○	○	○	○
Inspired	○	○	○	○	○
	Strongly Disagree	Mildly Disagree	Neither Agree nor Disagree	Mildly Agree	Strongly Agree
Nervous	○	○	○	○	○
Determined	○	○	○	○	○
Attentive	○	○	○	○	○
Jittery	○	○	○	○	○
Active	○	○	○	○	○
Afraid	○	○	○	○	○

APPENDIX 2

Positive and Negative Affect Scale-PANAS

Please read each statement and select the appropriate answer to indicate how much the statement applied to you **over the past week.** There are no right or wrong answers. Do not spend too much time on any statement.

	Did not apply to me at all	Applied to me to some degree, or some of the time	Applied to me a considerable degree, or a good part of the time	Applied to me very much, or most of the time
I found it hard to wind down.	○	○	○	○
I was aware of dryness of my mouth.	○	○	○	○
I couldn't seem to experience any positive feeling at all.	○	○	○	○
I experienced breathing difficulty (e.g., excessively rapid breathing; breathlessness in the absence of physical exertion).	○	○	○	○
I found it difficult to work up the initiative to do things.	○	○	○	○
I tended to over-react to situations.	○	○	○	○

	Did not apply to me at all	Applied to me to some degree, or some of the time	Applied to me a considerable degree, or a good part of the time	Applied to me very much, or most of the time
I experienced trembling (e.g., in the hands).	○	○	○	○
I felt that I was using a lot of nervous energy.	○	○	○	○
I was worried about situations in which I might panic and make a fool of myself.	○	○	○	○
I felt that I had nothing to look forward to.	○	○	○	○
I found myself getting agitated.	○	○	○	○
I found it difficult to relax.	○	○	○	○

	Did not apply to me at all	Applied to me to some degree, or some of the time	Applied to me a considerable degree, or a good part of the time	Applied to me very much, or most of the time
I felt down-hearted and blue.	○	○	○	○
I was intolerant of anything that kept me from getting on with what I was doing.	○	○	○	○
I felt I was close to panic.	○	○	○	○
I was unable to become enthusiastic about anything.	○	○	○	○
I felt I wasn't worth much as a person.	○	○	○	○
I felt that I was rather touchy.	○	○	○	○

	Did not apply to me at all	Applied to me to some degree, or some of the time	Applied to me a considerable degree, or a good part of the time	Applied to me very much, or most of the time
I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase; heart missing a beat).	○	○	○	○
I felt scared without any good reason.	○	○	○	○
I felt that life was meaningless.	○	○	○	○

APPENDIX 3
Semi-Structured Qualitative Interview Questionnaire

1) What information did you use to make your decision about the specific drug you'd prefer? Tell me about your thought process and reasoning. If you had all the time you wanted, what additional steps (if any) would you have taken before deciding?

2) How much sense were you able to make of the feedback form? What could have made it easier for you to understand? What other information would you like to have included beyond the list of medications?

3) From 0 – 100%, how likely would you be to seek medication if you were diagnosed with clinical anxiety? What else might you do to address your symptoms? Would you have any difficulty with or objections to staying on anti-anxiety medication for the rest of your life? Why or why not?

4) From 0 – 100%, how likely would you be to seek therapy if you were diagnosed with clinical anxiety? What factors would influence your decision to do so (or not do so)? Would you want to take medication at the same time? Between medication and therapy, do you view one of these approaches as superior? Why or why not?

5) Would your decision have been different if you didn't have the results of genetic testing but were presented with the same list of drugs? How so? What information would you use to make your decision in that case?

6) If this were a realistic situation, what else would you want to know? What kinds of emotional reactions would you likely have? What kinds of additional tests or interactions with healthcare providers would you want?

7) From 0 – 100%, how willing would you be to engage in genetic testing if your doctor recommended it? Does your opinion change in terms of what's being tested (for example, depression medication vs. likelihood of developing a terminal disease vs. learning about the characteristics you might pass on to your children)? What concerns do you have with the process of genetic testing in general? More specifically and hypothetically, what concerns would you have with using your own results in making important healthcare decisions? If there's anything that "feels" weird to you about this kind of testing I'd like to hear about that too.

8) Imagine the same situation we just talked through, but every single medication on your feedback form is in the "red" box (meaning they're all predicted to not work very well for you due to your genetic structure). How would that information affect you? In particular, what kinds

of emotional reactions might you have? What would you do to address your symptoms as a result of this information?

9) What else comes to mind that would help us understand people's reactions to this type of information and/or use of it in making healthcare decisions?

10) To what extent can people in your hometown get access to mental health services? What resources do you know of ?(psychiatrists, psychologists, counselors, etc.)

11) Do you travel to a different city for access to healthcare?

12) Assuming you have severe anxiety, where would you go to seek help? (Rank-Order Question)

a. Psychiatrist
b. Psychologist
c. Therapist
d. Your primary care physician
e. Seek advice from friends/family
f. Online resources

13) Follow up to #12: If you only had access to a primary care physician and a psychiatrist/psychologist was over an hour drive away, who would you choose to go to for your first visit regarding mental health services?

APPENDIX 4
Sample Decision Support Tool Dashboard
"Yellow Group"

Use as Directed	Use with Caution	Use with Increased Caution and with More Frequent Monitoring
Amitrypline (Elavil) Bupropion (Wellbutrin) Citalopram (Celexa) Mirtazapine (Remeron) Sertraline (Zoloft) Trazodone (Desyrel) Vilazodone (Viibryd)	Clomipramine (Anafranil) Desipramine (Norpramin) Desvenlafaxine (Pristiq) Escitalopram (Lexapro) Fluoxetine (Prozac) Fluvoxamine (Luvox) Nortriptyline (Pamelor)	Doxepin (Sinequan) Duloxetine (Cymbalta) Imipramine (Tofranil) Paroxetine (Paxil) Selegiline (Emsam) Venlafaxine (Effexor)

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